

STOCHASTIC INSULIN SENSITIVITY MODELS FOR TIGHT GLYCAEMIC CONTROL

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Abstract: Hyperglycaemia is prevalent in critical care, and tight control reduces mortality. Targeted glycaemic control can be achieved by frequent fitting and prediction of a modelled insulin sensitivity index, S_I . However, this parameter varies significantly in the critically ill as their condition evolves. A 3-D stochastic model of hourly S_I variability is constructed using retrospective data from 18 critical care patients. The model provides a blood glucose level probability distribution one hour following an intervention, enabling accurate prediction and more optimal glycaemic control. *Copyright © 2006 IFAC*

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1. INTRODUCTION

Hyperglycaemia and severe insulin resistance are prevalent in the critically ill, and tight control can reduce mortality up to 45% (Van den Berghe et al., 2001). Chase et al. (2005a) clinically verified a targeted control algorithm that accounts for inter-patient variability and evolving physiological condition. The adaptive control approach identifies patient dynamics, particularly insulin sensitivity, to determine the best control input. Hence better understanding and modelling of patient variability in the ICU can lead to better glycaemic management.

Therefore, the ultimate goal of this study is to produce model-base blood glucose confidence bands to optimise glycaemic control. These bands are based on stochastic models developed from clinically observed model-based variations, and allow targeted control with user specified confidence on the glycaemic outcome.

2. METHODS

2.1 Glucose-Insulin System Model

This study uses a patient-specific glucose-insulin system model from Chase et al. (2005a). It accounts for time-varying insulin sensitivity and endogenous glucose removal, and two saturation kinetics.

$$\dot{G} = -p_G G - S_I (G + G_E) \frac{Q}{1 + \alpha_G Q} + P(t) \quad (1)$$

$$\dot{Q} = -kQ + kI \quad (2)$$

$$\dot{I} = -n \frac{I}{1 + \alpha_I I} + \frac{u_{ex}(t)}{V_I} \quad (3)$$

where G and I denote the glucose above an equilibrium level, G_E , and the plasma insulin from an exogenous insulin input. Insulin utilization over time is Q , with effective insulin decay rate k . Endogenous glucose removal and insulin sensitivity are p_G and S_I . Insulin distribution volume is V_I , and n is plasma insulin decay. External nutrition and insulin input are $P(t)$ and $u_{ex}(t)$. Michaelis-Menten saturation in plasma insulin disappearance and insulin-stimulated glucose removal are defined by α_I and α_G .

Insulin sensitivity, S_I , is the critical parameter that drives the dynamic system response to exogenous insulin. This value changes with the severity of illness, and thus captures the evolution of the patient's insulin resistance and condition. Hence, identifying S_I over time is critical to providing safe, tight glycaemic control. It will also enable better prediction of the outcome of an intervention. However, no such models or data currently exist.

2.2 Stochastic Model

Patient-specific parameters, p_G and S_I , are fitted to long term retrospective clinical data from 18 patients from a 201-patients data audit (Shaw et al., 2004). Parameter identification is performed with an integration-based method developed by Hann et al. (2005). Each patient record spans at least one day with data every three-hours or less. This cohort broadly represents the cross section of patients seen in the ICU, regarding medical condition, age, sex, APACHE II scores and mortality.

Zero order piecewise linear functions are used to define p_G and S_I , with a discontinuity every two hours for p_G and every hour for S_I because greater variability in S_I is previously identified (Hann et al., 2005). Table 1 shows the parameter values (Chase et al., 2005a).

Table 1: Generic parameter values

Parameter	Unit	Value
a_G	L/mU	$1/65$
a_I	L/mU	0.0017
n	min^{-1}	0.16
k	min^{-1}	0.0198
V_I	L	3.15

The fitted p_G and S_I data reveals that the variability of both parameters is dependent on its present value. The distribution of fitted S_I is shown by the dots in Figure 1. The probability distribution of potential S_I , shown by the probability bands, clearly varies with its value across the horizontal axis.

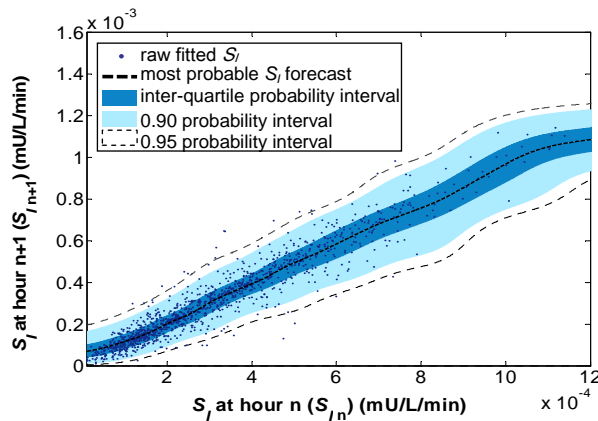


Figure 1: Fitted S_I and probability intervals

Thus, the variations in S_I can be treated as a Markov process. A Markov process has the property that the conditional probability distribution of future states of the process, given the present state, depends only upon the current state. Therefore, using the Markov property of the stochastic behaviour of S_I , the conditional probability distribution of $S_{I_{n+1}}$ taking on a value y can be calculated by knowing $S_{I_n} = x$:

$$P(S_{I_{n+1}} = y | S_{I_n} = x) = \frac{P(S_{I_n} = x, S_{I_{n+1}} = y)}{P(S_{I_n} = x)} \quad (4)$$

Considering the fitted S_I in a 2-D space, as shown in Figure 1, the joint probability function across the x - y ($S_{I_n} - S_{I_{n+1}}$) plane is defined by the fitted values shown by the dots whose coordinates are x_i and y_i ,

$$P(x, y) = \frac{1}{n} \sum_{i=1}^n \frac{\phi(x; x_i, \sigma_{x_i}^2)}{p_{x_i}} \frac{\phi(y; y_i, \sigma_{y_i}^2)}{p_{y_i}} \quad (5)$$

$$p_{x_i} = \int_0^\infty \phi(x; x_i, \sigma_{x_i}^2) \quad (6)$$

$$p_{y_i} = \int_0^\infty \phi(y; y_i, \sigma_{y_i}^2) \quad (7)$$

Effectively, the 2-D joint probability function is the normalised summation of normal probability distribution functions $\phi(x; x_i, \sigma_{x_i}^2)$ centred at individual data points.

To illustrate a 3-D map in the mind, consider this numerical operation as a sand building exercise. If the first quadrant of the x - y ($S_{I_n} - S_{I_{n+1}}$) plane, as shown in Figure 1, is where the sand box is confined in, and that a pile of sand of a cubic unit is dropped onto every dot in Figure 1, then the resulted sand sculpture is the simple representation of the joint probability $P(x, y)$ on the x - y ($S_{I_n} - S_{I_{n+1}}$) plane. In Equations (5)-(7), the variance σ at each data point is a function of the local data density in a centred and orthonormalised space of x and y . Putting Equations (6) and (7) into Equation (5) normalises each $\phi(x; x_i, \sigma_{x_i}^2)$ and $\phi(y; y_i, \sigma_{y_i}^2)$ in the positive domain. This, in the sand building exercise example, effectively puts boundaries along $x = 0$ and $y = 0$, confining sand to stay in the first quadrant, and therefore forces physiological validity in S_I values.

In Equation (4), the right hand side denominator can be calculated by integrating Equation (5) with respect to y . Hence, Equation (5) can be calculated:

$$P(S_{I_{n+1}} = y | S_{I_n} = x) = \sum_{i=1}^n \omega_i(x) \frac{\phi(y; y_i, \sigma_{y_i}^2)}{p_{y_i}} \quad (8)$$

$$\omega_i(x) = \frac{\phi(x; x_i, \sigma_{x_i}^2) / p_{x_i}}{\sum_{j=1}^n \phi(x; x_j, \sigma_{x_j}^2) / p_{x_j}} \quad (9)$$

Thus, knowing $S_{I,n} = x$ at hour n , the probability of $S_{I,n+1} = y$ at hour $n+1$ can be calculated using Equations (8) and (9). The probability intervals shown in Figure 1 are also calculated from integrating Equation (8). Plotting Equation (8) across the x - y ($S_{I,n} - S_{I,n+1}$) plane, the resulting 3-D stochastic model is shown in Figures 2 and 3.

The same numerical operations described in Equations (4)-(9) also apply to p_G , producing similar results. However the probability density across the x - y plane is highly concentrated along the line $y = x$, almost to the exclusion of other points. This result reinforces the idea that p_G is effectively constant, even though patient specific (Hann et al., 2005). Hence, variability of p_G is neglected in this study and $p_G = 0.01$ used (Hann et al., 2005).

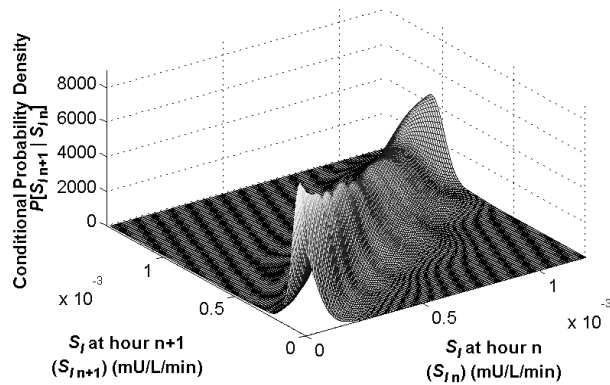


Figure 2: Three-dimensional S_I stochastic model

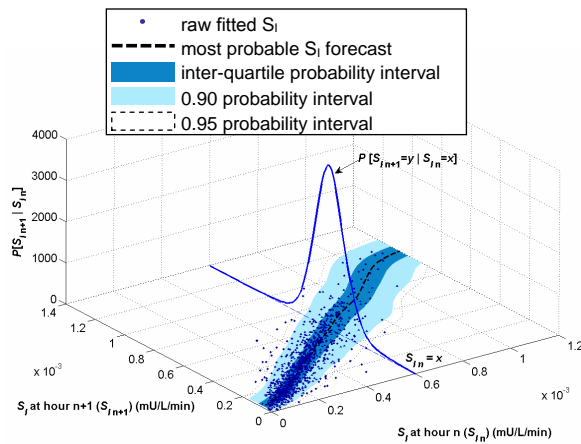


Figure 3: Conditional probability distribution

The stochastic parameter model developed can be integrated into the model of Equations (1)-(3), defining the blood glucose level probability distribution one hour following a known insulin and/or nutrition intervention. This distribution can then be used to adjust a target glucose value for the subsequent hour to ensure a probability of exceedance for the resulting glucose level. The stochastic model therefore enables more knowledgeable predictions

with defined probability distributions for the outcomes of glycaemic control inputs.

2.3 Model Validation with Clinical Trial Data

The stochastic model developed from the 18-patients cohort is evaluated on 8 clinical control trials (Wong et al., 2006). This data is independent from the cohort used to develop the stochastic model. The trials performed consisted of hourly cycles of the following steps:

1. Measure blood glucose levels.
2. Fit p_G and S_I to the measured blood glucose.
3. Determine new control intervention to achieve a blood glucose target level.
4. Implement control intervention.

To assess the stochastic model, these 8 trials are numerically re-enacted with control interventions as given in the trial but with step 3 of the trial cycle modified to include the use of the model and confidence bands it generates for an intervention:

- 3a. Generate potential S_I probability intervals from the time-average identified S_I of the fitted time interval using the stochastic model.
- 3b. Calculate blood glucose confidence intervals with respect to the S_I probability intervals using the numerical model in Equations (1)-(3).

This test allows validation of the model in a clinical control scenario. The resulting outputs are validated based on how well the resulting clinical data fit the predicted distributions for the clinical trial patient. More specifically, it is a means of assessing whether, for example, the 90% confidence band delivered by the model captures 90% of the results.

2.4 Application as Virtual Patient

Finally, the model can be used to create virtual patients by using the Markov model to create a time-varying profile for S_I . In combination with the model of Equations (1)-(3) this stochastic model can then be used, with constraints on the limits for S_I , to test or develop control protocols in simulated clinical trials. All that is required is an initial value and a validated stochastic model to ensure realistic behaviour for the virtual patients.

3. RESULTS AND DISCUSSION

3.1 Comparison to Clinical Trial Data

Blood glucose probability intervals were produced at each control intervention in the 8 clinical trials and

compared to measured blood glucose levels one hour later. The results are shown in Table 2. Detailed results from Trial 4 are shown Figure 4.

Table 2: Retrospective probabilistic assessment on clinical control trials

Clinical control patients	Number of interventions made	Measurement error within inter-quartile probability interval	Measurement error within 0.90 probability interval
1	9	6 (67%)	9 (100%)
2	9	5 (56%)	7 (78%)
3	9	5 (56%)	8 (89%)
4	9	5 (56%)	7 (78%)
5	9	9 (100%)	9 (100%)
6	9	9 (100%)	9 (100%)
7	9	8 (89%)	9 (100%)
8	23	16 (70%)	23 (100%)
total	86	63 (73%)	81 (94%)

The top panel of Figure 4 displays blood glucose, where the crosses are the actual clinical measurements with 7% measurement error, the solid line is the fitted blood glucose profile, and the circles are the most likely probabilistic blood glucose predictions following control interventions. The 90% band and inter-quartile probability ranges are shown by the bars. The bottom panel shows the fitted S_I value, its most probable value, and its probabilistic bounds, as produced by the stochastic model. Note that only the prior hour's value of S_I is required to find the distribution.

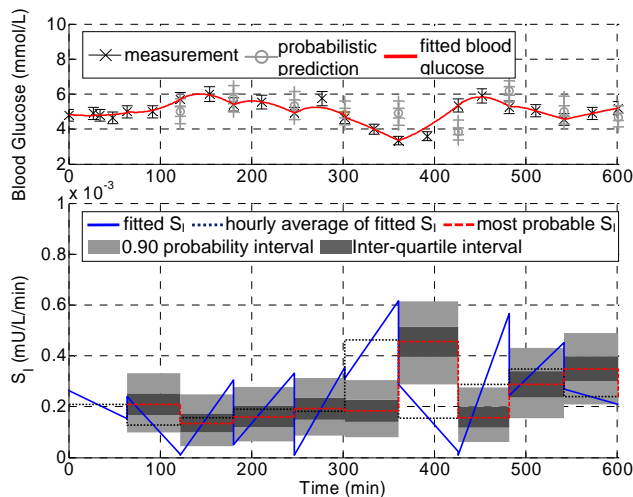


Figure 4: Simulated clinical control trial on Patient 4

Patient 4's blood glucose briefly dropped below 4 mmol/L during the trial at approximately 360mins, which was not accounted for in the probabilistic forecast. Given the identified Patient 4 S_I profile, different control interventions were explored. In particular, the S_I stochastic model and 90% bounds are used to assist decision making. A comparison between the clinical trial and simulated new control intervention results is shown in Figure 5.

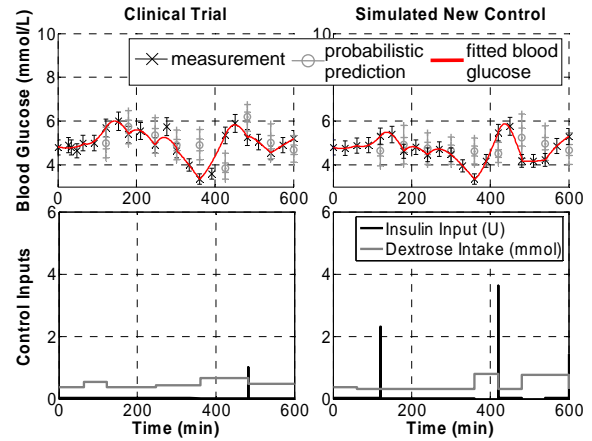


Figure 5: Clinical trial vs. simulated new control results on Patient 4

In Figure 5, the re-simulated control aimed to maintain the glycaemic levels above 4 mmol/L with 90% probability. This use of the stochastic distribution from the model enabled the subsequent two hourly targets to be reset using that data. As a result, more aggressive interventions were issued in the first half of the simulated trial, achieving more tightly controlled glycaemic levels.

The brief blood glucose excursion below 4 mmol/L was still unavoidable because the S_I variation exceeded the 0.90 confidence limit at 300-360mins. However, a more vigorous remedy was taken at 360 minutes in the simulated trial to obtain a 0.90 confidence in blood glucose above 4 mmol/L in an hour. This first intervention was a large feed change as seen in Figure 4. It was followed by an aggressive insulin bolus to counter the sudden feed change the hour prior. Overall, the S_I stochastic model can be used to deliver tighter, safer glycaemic management and improve control intervention selection.

Across all 8 patients, the S_I stochastic model successfully captures the identified S_I variation trend, accounting for 94% of measurements over time within the 0.90 confidence band, and 73% with a 0.50 confidence. Hence, the model may be slightly conservative in this respect where the 7% measurement error is considered.

However, if just the measured values are used from the trials the results are closer to exact. Specifically, 48% of explicit measurement values were in the 0.50 band and 87% were in the 0.90 band. Thus, without accounting for measurement error the model is slightly in error, which may be due to the limited number of measurements, the first order Markov model employed, or both.

Overall, it is worth noting that when S_I increases, the blood glucose level probability interval tightens, as seen in Figures 1-2. The wider range of uncertainties in blood glucose levels associated with low S_I reflects

the risk of hypoglycaemic events for highly insulin resistant patients under intensive insulin therapy (Amiel et al., 1987). This situation was specifically seen in Patient 4, whose identified S_I profile is in the lower physiological range.

3.2 Virtual Trial Application and Analysis

“Virtual patients” with p_G and S_I following the stochastic behaviour of the Markov model developed reflect typical critical care patient conditions. A virtual cohort of $n = 200$ patients was created and tested in simulated trials. Initial conditions for these virtual patients, including starting blood glucose levels, initial S_I levels, insulin infusion, dextrose infusion etc., were randomly chosen to represent typical critical care situations. Resulting blood glucose probability intervals from control inputs are produced with each control intervention. The simulated trials each span 24 hours. Therefore, 23 hourly blood glucose measurements (excluding the starting blood glucose levels) were analysed against the probability intervals. The results from the simulated trials are summarised in Table 3.

Table 3: Virtual patient trials summary

	Glucose < 4 mmol/L	Glucose in 50% band (%)	Glucose in 90% band (%)
Max	22%	96%	100
Mean	2.5%	77%	95%
Min	0%	52%	78%
SD	4%	9%	4.5%

The virtual cohort produced results that are similar to the 8 clinical trials. The inter-quartile confidence intervals covered 77% of blood glucose measurements, and the 0.90 confidence intervals covered 95%. The defined hypoglycaemic level for the trials was 4 mmol/L.

All control interventions maintained a minimum of 0.90 confidence level in the resulting blood glucose levels being above 4 mmol/L. Across the 200 virtual patients cohort, 2 measurements (0.04%) fell below 3 mmol/L, and 111 (2.5%) fell below 4 mmol/L. These slightly hypoglycaemic events all occurred when S_I took a sudden rise that exceeded the 0.90 probability intervals in S_I .

The loss of control with large swings outside the 90% likelihood of occurrence, further illustrates the meaning of this bound. In particular, the size of such swings, especially at low insulin sensitivity, indicates the size of the change required to be outside the 90% likelihood of occurrence. In contrast, the width of these bounds also indicates that 10% of the time patients can take sudden, quite drastic swings in

insulin sensitivity. These quite drastic swings would be due to equally significant changes in patient condition. Hence, the metric may be worth monitoring on its own as a guide to patient condition. From a control standpoint, the targeted, confidence interval based control algorithm was able to maintain blood glucose levels within the 4-6 mmol/L band 70% of the time once the blood glucose levels were brought into this range. This value exceeds clinical simulations without confidence bands (Wong et al., 2005). For those patients whose blood glucose levels were reduced to 4-6 mmol/L ($n = 159$) during the 24-hour simulated trial, 125 (78.62%) stayed in the band more than 50% of the time, and 78 (50.94%) stayed in the band more than 75% of the time.

More notably, out of the cohort of 200 virtual patients, 41 (20.50%) never achieved normoglycemia in the 4-6 mmol/L band at any instance during the 24 hours trial due to insulin resistance and insulin effect saturation. These patients have virtual S_I profiles generally in the very low physiological range. Consequently, insulin-stimulated glucose removal was constantly saturated with high insulin doses, and the blood glucose confidence bands are also wide.

These results indicated that to always maintain a 0.90 confidence level against a hypoglycaemic event, the achievable blood glucose reduction is limited in some cases. In particular, very low insulin sensitivity and wide 0.90 bands will hinder the ability to remain in the 4-6 mmol/L band under control, while also ensuring a 90% confidence of no hypoglycaemic events. As a result, the glucose levels are higher. These results match clinical observations that blood glucose levels under control are more volatile in highly insulin resistant patients (Chase et al., 2005b; Hann et al., 2005; Wong et al., 2006).

The average number of hours taken for the blood glucose levels to be reduced to within 4-6 mmol/L from the start of the trial was 8.3 (SD ± 8.91) hours. Hence, the time taken to get into the band for a hyperglycaemic patient can be quite high if they are highly insulin resistant. This result highlights the need to take early action at the emergence of hyperglycaemia in critical care.

3.3 Results and Discussion Summary

The glucose-insulin system model, together with the integral-based parameter identification, can effectively capture critical care patient behaviour. In addition, the stochastic model further enhances the ability to predict, as well as imitate, typical critical care patient dynamics. The incorporation of the stochastic model into the numerical glucose-insulin system can also be used to create “virtual patients”, creating a platform to experiment with different clinical control protocols based on clinically observed patient dynamics and evolution.

Overall, higher identified S_I levels result in tighter blood glucose probability intervals, making tighter control easier with less control effort. It is worth noting that less critically ill patients, by APACHE II or other score, are also typically less insulin resistant and hyperglycaemic (e.g. Christiansen et al., 2004; Mentula et al., 2005). Therefore, a less critically ill cohort is potentially much more likely to be easier to control in terms of variability. This result could thus be used to help compare results of different protocols on different types of patient cohorts.

4. CONCLUSIONS

The stochastic model presented defines the variation of critical care patient insulin sensitivity for the system model presented. As a result, the distribution of blood glucose levels one hour following a known insulin and/or nutrition intervention can be determined and used to enhance control, by enabling more knowledgeable and accurate prediction. The stochastic model thus acts as a tool to assist clinical intervention decisions, maximising the probability of achieving the desired tight glycaemic regulation while maintaining patient safety. The same stochastic model can also be used to create realistic, validated virtual patients for developing new control protocols.

More generally, application of this model also offers new insights. In particular, the model shows that less critically ill cohorts, who are also less insulin resistant, have tighter variation in insulin sensitivity. Such cohorts would be easier to control and shed light on the different results obtained in landmark glycaemic control studies with very different cohorts in terms of APACHE II score and level of critical illness. Overall, the model allows the impact of control inputs on blood glucose levels to be statistically assessed, providing further confidence in the effectiveness of the control protocol utilised against evolving patient dynamics.

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